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(PATENT)

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In re Patent Application of:  
Halina MILLER-PODRAZA et al.

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: July 19, 2004

Art Unit: N/A

For: NOVEL BINDING EPITOPES FOR  
HELCOBACTER PYLORI AND USE  
THEREOF

Examiner: Not Yet Assigned

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

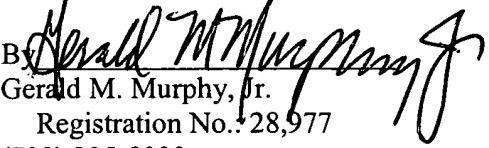
The PTO is requested to use the amended sheets/claims attached hereto (which correspond to Article 19 amendments or to claims attached to the International Preliminary Examination Report (Article 34)) during prosecution of the above-identified national phase PCT application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: July 19, 2004

GMM/smt

Respectfully submitted,

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Attachment(s)

What is claimed:

1. A *Helicobacter pylori* binding substance comprising oligosaccharide sequence

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[Hex1(A)<sub>q1</sub>(NAc)<sub>r1</sub>α/β3]<sub>s</sub>Gal(NAc)<sub>r2</sub>β4Glc(A)<sub>q2</sub>(NAc)<sub>r3</sub>

wherein q1,q2, r1, r2, r3, and s are each independently 0 or 1 so that at least r2 or q2 is 1;

10

Hex1 is galactose (Gal), glucose (Glc) or mannose (Man);

15

and analogs or derivatives of said oligosaccharide sequence having binding activity to *Helicobacter pylori* for the prophylaxis or treatment of any condition due to the presence of *Helicobacter pylori* in a subject.

2. The substance according to claim 1, wherein said sequence is terminal.

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3. The *Helicobacter pylori* binding substance according to claim 1 or 2 further comprising β6Hex3(NAc)<sub>r5</sub> or β3Hex3(NAc)<sub>r5</sub> structure in the reducing end of the oligosaccharide sequence forming the following structure

[Hex1(A)<sub>q1</sub>(NAc)<sub>r1</sub>α/β3]<sub>s</sub>Gal(NAc)<sub>r2</sub>β4Glc(A)<sub>q2</sub>(NAc)<sub>r3</sub>β6/β3Hex3(A)<sub>r4</sub>(NAc)<sub>r5</sub>

25

wherein q1,q2, r1, r2, r3, s, and Hex1 are as defined in claim 1; r4 and r5 are independently 0 or 1; Hex3 is mannose (Man), galactose (Gal) or glucose (Glc).

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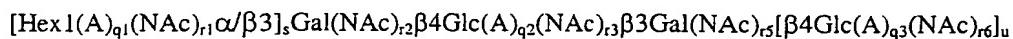
4. A *Helicobacter pylori* binding substance comprising oligosaccharide sequence

Glc(A)<sub>q1</sub>(NAc)<sub>r1</sub>β3Galβ4Glc(NAc)<sub>r3</sub>β6Hex3(NAc)<sub>r5</sub>

wherein q1, r1, and r3 are as defined in claim 1; r5 and Hex3 are as defined in claim 3.

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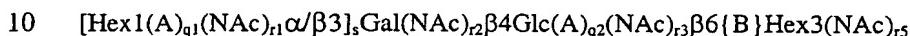
5. The *Helicobacter pylori* binding substance according to claim 1 or 2 further comprising β3Gal(NAc)<sub>r5</sub>[β4Glc(A)<sub>q3</sub>(NAc)<sub>r6</sub>]<sub>u</sub> structure in the reducing end of the oligosaccharide sequence forming the following structure



wherein q1,q2, r1, r2, r3, s, and Hex1 are as defined in claim 1; r5 is as defined in claim 2, q3, r6, and u are independently 0 or 1.

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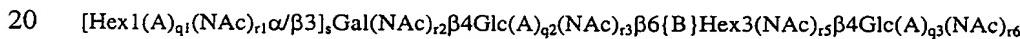
6. The *Helicobacter pylori* binding substance according to claim 1 or 2 further comprising  $\beta6\{B\}\text{Hex3(NAc)}_{r5}$  structure in the reducing end of the oligosaccharide sequence forming the following structure



wherein q1,q2, r1, r2, r3, s, and Hex1 are as defined in claim 1; B is branch structure  $\text{Hex2(NAc)}_{r4}\beta3$ , Hex2 and Hex 3 are independently mannose (Man), galactose (Gal) or glucose (Glc), r5 is independently 0 or 1.

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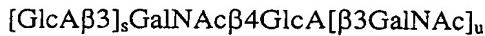
7. The *Helicobacter pylori* binding substance according to claim 1 or 2 further comprising  $\beta6\{B\}\text{Hex3(NAc)}_{r5}[\beta4\text{Glc(A)}_{q3}(\text{NAc})_{r6}]_u$  structure in the reducing end of the oligosaccharide sequence forming the following structure



wherein q1,q2, r1, r2, r3, s, and Hex1 are as defined in claim 1; B is as defined in claim 4, q3 and r6 are independently 0 or 1.

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8. The *Helicobacter pylori* binding substance according to claim 1 or 2, wherein said oligosaccharide sequence is a natural type chondroitin sequence according to the following structure

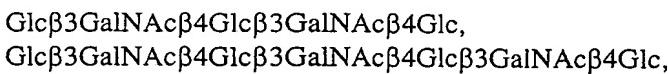


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wherein s and u are as defined above with the proviso that either s or u is 1.

9. A *Helicobacter pylori* binding substance comprising one or several of the following oligosaccharide sequences

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Glc $\beta$ 3GalNAc $\beta$ 4Glc $\beta$ 3GalNAc,  
Glc $\beta$ 3GalNAc $\beta$ 4Glc $\beta$ 3GalNAc $\beta$ 4Glc $\beta$ 3GalNAc,  
Glc $\beta$ 3GalNAc $\beta$ 4Glc $\beta$ 3GalNAc $\beta$ 4Glc $\beta$ 3GalNAc $\beta$ 4Glc $\beta$ 3GalNAc,

- 5 Glc $\beta$ 3GlcNAc $\beta$ 4Glc,  
Glc $\beta$ 3GlcNAc $\beta$ 4Glc $\beta$ 3GlcNAc $\beta$ 4Glc,  
Glc $\beta$ 3GlcNAc $\beta$ 4Glc $\beta$ 3GlcNAc $\beta$ 4Glc $\beta$ 3GlcNAc $\beta$ 4Glc,  
Glc $\beta$ 3GlcNAc $\beta$ 4Glc $\beta$ 3GlcNAc,  
Glc $\beta$ 3GlcNAc $\beta$ 4Glc $\beta$ 3GlcNAc $\beta$ 4Glc $\beta$ 3GlcNAc, and  
10 Glc $\beta$ 3GalNAc $\beta$ 4Glc $\beta$ 3GlcNAc $\beta$ 4Glc $\beta$ 3GlcNAc $\beta$ 4Glc $\beta$ 3GlcNAc

10. A *Helicobacter pylori* binding substance comprising one or several of the following oligosaccharide sequences

- 15 GlcNAc $\beta$ 3Gal $\beta$ 4GlcNAc $\beta$ 6GlcNAc,  
Glc $\beta$ 3Gal $\beta$ 4GlcNAc $\beta$ 6GlcNAc,  
GlcA $\beta$ 3Gal $\beta$ 4GlcNAc $\beta$ 6GlcNAc,  
GlcNAc $\beta$ 3Gal $\beta$ 4GlcNAc $\beta$ 6GalNAc,  
Glc $\beta$ 3Gal $\beta$ 4GlcNAc $\beta$ 6GalNAc,  
20 GlcA $\beta$ 3Gal $\beta$ 4GlcNAc $\beta$ 6GalNAc,  
GlcNAc $\beta$ 3Gal $\beta$ 4GlcNAc $\beta$ 6Gal,  
Glc $\beta$ 3Gal $\beta$ 4GlcNAc $\beta$ 6Gal, and  
GlcA $\beta$ 3Gal $\beta$ 4GlcNAc $\beta$ 6Gal  
25 11. The *Helicobacter pylori* binding substance according to claim 1 or 2 comprising one or several of the following oligosaccharide sequences

- GlcA $\beta$ 3GalNAc $\beta$ 4GlcA,  
GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA,  
30 GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA, and  
GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA

- 35 12. The *Helicobacter pylori* binding substance according to claim 1 or 2 comprising one or several of the following oligosaccharide sequences

GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA,  
GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA,

GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA,

GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc,

GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc, and

5 GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc $\beta$ 4GlcA $\beta$ 3GalNAc

13. The *Helicobacter pylori* binding substance according to claim 1 or 2 comprising at least one of the following oligosaccharide sequence

10 GalNAc $\beta$ 4Glc,

Gal $\beta$ 4GlcA, and

GalNAc $\beta$ 4GlcA

14. The *Helicobacter pylori* binding substance according to any one of claims 1 – 13, 15 wherein the substance is conjugated to a polysaccharide, preferably to a polylactosamine chain or a conjugate thereof.

15. The *Helicobacter pylori* binding substance according to any one of claims 1 – 13, wherein the substance is a glycolipid.

20 16. The *Helicobacter pylori* binding substance according to any one of claims 1 – 13, wherein the substance is an oligomeric molecule containing at least two or three oligosaccharide chains.

25 17. The *Helicobacter pylori* binding substance consisting of a micelle comprising one or more of the substances of any one of claims 1 – 16.

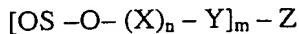
30 18. The *Helicobacter pylori* binding substance according to any one of claims 1 – 17, wherein the substance(s) is/are conjugated to a carrier.

19. The *Helicobacter pylori* binding substance according to any one of claims 1 - 18, wherein the substance is covalently conjugated with an antibiotic effective against *Helicobacter pylori*, preferably a penicillin type antibiotic.

35 20. The *Helicobacter pylori* binding substance or a mixture of substances according to any one of claims 1 – 18, wherein position C1 of reducing end terminal Glc or GlcNAc of the oligosaccharide sequence (OS) is oxygen linked (-O-) to an

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oligovalent or a polyvalent carrier (Z), via a spacer group (Y) and optionally via a monosaccharide or oligosaccharide residue (X), forming the following structure



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where integers m, and n have values m = 1, and n is independently 0 or 1; X is preferably lactosyl-, galactosyl-, poly-N-acetyl-lactosaminyl, or part of an O-glycan or an N-glycan oligosaccharide sequence, Y is a spacer group or a terminal conjugate such as a ceramide lipid moiety or a linkage to Z;

10

or an analog or a derivative of the substance of said structure having binding activity to *Helicobacter pylori*.

21. The substance according to any one of claims 1 - 20 for use as a *Helicobacter pylori* binding or inhibiting substance.

22. The substance according to any one of claims 1 - 20 for use as a medicament.
23. Use of the substance according to any one of claims 1 - 20 for the production of a composition having *Helicobacter pylori* binding or inhibiting activity.
24. Use of the substance according to any one of claims 1 - 20 for the production of a pharmaceutical composition for the treatment of any condition due to the infection of *Helicobacter pylori*.

25

25. A pharmaceutical composition comprising the substance according to any one of claims 1 - 20 for the treatment of any condition due to the presence of *Helicobacter pylori*.
- 30 26. The pharmaceutical composition according to claim 25, for the treatment of chronic superficial gastritis, gastric ulcer, duodenal ulcer, gastric adenocarcinoma, non-Hodgkin lymphoma in human stomach, liver disease, pancreatic disease, skin disease, heart disease, or autoimmune diseases including autoimmune gastritis and pernicious anaemia and non-steroid anti-inflammatory drug (NSAID) related gastric disease, or for prevention of sudden infant death syndrome.

- 35 27. A method for the treatment of a condition due to presence of *Helicobacter pylori*, wherein a pharmaceutically effective amount of the substance according to any one

of claims 1 – 20 or the composition according to claims 25 or 26 is administered to a subject in need of such treatment.

28. The method according to claim 27, when said condition is caused by the presence  
5 of *Helicobacter pylori* in the gastrointestinal tract of a patient.

29. The method according to claim 27, for the treatment of chronic superficial gastritis, gastric ulcer, duodenal ulcer, gastric adenocarcinoma, non-Hodgkin lymphoma in human stomach, liver disease, pancreatic disease, skin disease, heart  
10 disease, or autoimmune diseases including autoimmune gastritis and pernicious anaemia and non-steroid anti-inflammatory drug (NSAID) related gastric disease, or for prevention of sudden infant death syndrome.

30. Use of the substance according to any one of claims 1 - 20, for the diagnosis of a  
15 condition due to infection by *Helicobacter pylori*.

31. A nutritional additive or composition containing the substance according to any one of claims 1 - 20.

20 32. The nutritional additive or composition according to claim 31 for use in infant food.

33. Use of the substance according to any one of claims 1 – 20, for the identification of bacterial adhesin.

25 34. Use of the substance according to any one of claims 1 – 20 or a substance identified according to claim 33, for the production of a vaccine against *Helicobacter pylori*.

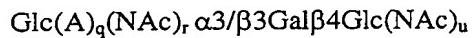
30 35. Use of the substance according to any one of claims 1 – 20, for typing *Helicobacter pylori*.

36. The substance according to any one of claims 1 – 20, for use in *Helicobacter pylori* binding assays.

35 37. A *Helicobacter pylori* binding substance comprising an oligosaccharide sequence according to Formula 9

5 wherein integers l, m, and n have values m = 1, l and n are independently 0 or 1; R<sub>1</sub> is H and R<sub>2</sub> is OH, or R<sub>1</sub> is OH and R<sub>2</sub> is H, or R<sub>1</sub> is H and R<sub>2</sub> is a monosaccharidyl- or oligosaccharidyl- group, preferably a beta glycosidically linked galactosyl group, R<sub>3</sub> is independently -OH or acetamido (-NHCOCH<sub>3</sub>) or an acetamido analogous group, R<sub>7</sub> is acetamido (-NHCOCH<sub>3</sub>) or an acetamido analogous group; when l = 1, R<sub>4</sub> is -H and R<sub>5</sub> is oxygen linked to bond R<sub>6</sub> and forms a beta anomeric glycosidic linkage to saccharide B, or R<sub>5</sub> is -H and R<sub>4</sub> is oxygen linked to bond R<sub>6</sub> and forms an alpha anomeric glycosidic linkage to saccharide B; when l = 0, R<sub>6</sub> is -OH linked to B; X is monosaccharide or oligosaccharide residue, X is lactosyl-, galactosyl-, poly-N-acetyl-lactosaminyl, or part of an O-glycan or an N-glycan oligosaccharide sequence; Y is a spacer group or a terminal conjugate such as a ceramide lipid moiety or a linkage to Z; Z is an oligovalent or a polyvalent carrier; the oxygen linkage (-O-) between position C1 of the B saccharide and saccharide residue X or spacer group Y can be replaced by carbon (-C-), nitrogen (-N-) or sulphur (-S-) linkage; R<sub>8</sub> and R<sub>9</sub> are independently carboxylic acid amide, such as methylamide or ethylamide, hydroxymethyl (-CH<sub>2</sub>-OH) or a carboxylic acid group or an ester thereof, such as methyl or ethyl ester; R<sub>3</sub>, R<sub>7</sub>, and R<sub>10</sub> are independently hydroxyl, acetamido or acetamido group mimicking group, such as C<sub>1-6</sub> alkyl-amides, arylamido, secondary amine, preferentially N-ethyl or N-methyl, O-acetyl, or O-alkyl for example O-ethyl or O-methyl.

25 38. A *Helicobacter pylori* binding substance comprising an oligosaccharide sequence



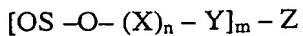
30 wherein q, r and u are independently 0 or 1,

with the proviso that when said oligosaccharide sequence contains β3 linkage, both q and r are 0 or 1; or

35  $\text{GalA(NAc)}_r \alpha 3/\beta 3 \text{Gal} \beta 4 \text{Glc(NAc)}_u$

wherein r and u are independently 0 or 1, and *Helicobacter pylori* binding analogs and derivatives thereof.

39. A *Helicobacter pylori* binding non-acidic polyvalent substance comprising the  
5 oligosaccharide sequence as defined in any one of claims 1-19, wherein said  
oligosaccharide sequence (OS) is a part of structure



- 10 as defined in claim 20, Y being a hydrophilic spacer, more preferably a flexible hydrophilic spacer, and *Helicobacter pylori* binding analogs and derivatives thereof.

40. The *Helicobacter pylori* binding non-acidic polyvalent substance according to  
claim 39, wherein linker structure Y is

- 15  $[\text{OS} - \text{O} - (\text{X})_n - \text{L}_1 - \text{CH}(\text{H}/\{\text{CH}_{1-2}\text{OH}\}_{p_1}) - \{\text{CH}_1\text{OH}\}_{p_2} - \{\text{CH}(\text{NH}-\text{R})\}_{p_3} - \{\text{CH}_1\text{OH}\}_{p_4} - \text{L}_2]_m - \text{Z}$

wherein L<sub>1</sub> and L<sub>2</sub> are linking groups comprising independently oxygen, nitrogen,  
sulphur or carbon linkage atom or two linking atoms of the group forming linkages  
20 such as -O-, -S-, -CH<sub>2</sub>-, -N-, -N(COCH<sub>3</sub>)-, amide groups -CO-NH- or -NH-CO- or  
-N-N- (hydrazine derivative) or an amino oxy-linkages -O-N- and -N-O-; L<sub>1</sub> is  
linkage from carbon 1 of the reducing end monosaccharide of X or when n = 0, L<sub>1</sub>  
replaces -O- and links directly from the reducing end C1 of OS; p<sub>1</sub>, p<sub>2</sub>, p<sub>3</sub>, and p<sub>4</sub>  
are independently integers from 0-7, with the proviso that at least one of p<sub>1</sub>, p<sub>2</sub>, p<sub>3</sub>,  
25 and p<sub>4</sub> is at least 1; CH<sub>1-2</sub>OH in the branching term {CH<sub>1-2</sub>OH}<sub>p<sub>1</sub></sub> means that the  
chain terminating group is CH<sub>2</sub>OH and when the p<sub>1</sub> is more than 1 there is secondary  
alcohol groups -CHOH- linking the terminating group to the rest of the spacer; R is  
preferably acetyl group (-COCH<sub>3</sub>) or R is an alternative linkage to Z and then L<sub>2</sub> is  
one or two atom chain terminating group, in another embodiment R is an analog  
30 forming group comprising C<sub>1-4</sub> acyl group comprising amido structure or H or C<sub>1-4</sub>  
alkyl forming an amine; and m > 1 and Z is polyvalent carrier; OS and X are as  
defined in claim 13.

41. A *Helicobacter pylori* binding substance comprising the oligosaccharide sequence



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wherein q, r and u are each independently 0 or 1, with the proviso that said oligosaccharide sequence is not  $\text{Gal} \alpha 3 \text{Gal} \beta 4 \text{Glc/GlcNAc}$ ,

as a non-reducing end terminal sequence, and *Helicobacter pylori* binding analogs  
10 and derivatives thereof.

42. The substance according to any one of claims 38-41 for use in binding bacteria,  
toxins or viruses.

15 43. The substance according to any one of claims 38-41 for use as a medicament.

44. A method for the treatment of a condition due to presence of *Helicobacter pylori*,  
wherein a pharmaceutically effective amount of the substance as defined in any one  
of claims 1 – 20 or 38-41 is administered to a subject in need of such treatment.

20 45. The method according to claim 44, when said condition is caused by the presence  
of *Helicobacter pylori* in the gastrointestinal tract of a patient.

46. The method according to claim 44, for the treatment of chronic superficial  
gastritis, gastric ulcer, duodenal ulcer, gastric adenocarcinoma, non-Hodgkin

25 lymphoma in human stomach, liver disease, pancreatic disease, skin disease, heart  
disease, or autoimmune diseases including autoimmune gastritis and pernicious  
anaemia and non-steroid anti-inflammatory drug (NSAID) related gastric disease, or  
for prevention of sudden infant death syndrome.

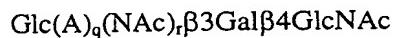
30 47. The method of treatment according to any one of claims 44-46, wherein said  
substance is a nutritional additive or a part of a nutritional composition.

48. The substance according to claim 42, wherein said toxin is toxin a of *Clostridium*  
*difficile*.

35

49. The substance according to any one of claims 41-43, wherein said oligosaccharide sequence is  $\beta$ 1-6 linked from the reducing end to GalNAc, GlcNAc, Gal or Glc.

5 50. The substance according to any one of claims 41-43, wherein said oligosaccharide sequence is



10 q and r being as defined in claim 41.

51. A method of screening *Helicobacter pylori* binding substances comprising

- modifying at least one hydroxyl or acetamido group of an oligosaccharide sequence  
15 as defined in any one of claims 1-20 into another chemical group

- determining *Helicobacter pylori* binding or inhibiting substances from the modified oligosaccharide sequences

20 52. A functional food comprising substances according to any of the claims 1-20 or 41.

53. A functional food comprising substances according to any of the claims 9-13

25 54. A functional food according to claim 52 or 53, wherein said food is a beverage.

55. A functional food according to claim 52 or 53, wherein said food is an infant formula.

30 56. A functional food according to claim 52 or 53, wherein said food is animal feed.

57. A method of producing chondroitin oligosaccharides from chondroitin sulphates comprising

- removing sulphates from chondroitin sulphate by chemical hydrolysis  
35 - specifically hydrolyzing glycosidic bonds between GalNAc and GlcA

58. The method of claim 57, wherein the hydrolysis is performed by acid hydrolysis, preferably by a strong carboxylic acid.

59. The method of claim 57, wherein said strong carboxylic acid is trifluoroacetic acid.

5

60. The method of claim 57 further comprising a step of purification involving anion exchange chromatography and/or gel filtration chromatography (size exclusion chromatography).

10 61. A method for production of amidated glucuronic acid comprising oligosaccharides and monosaccharides from glucuronic acid comprising polysaccharides selected from the group consisting of desulphated chondroitin sulphate, hyaluronic acid and bacterial exopolysaccharide comprising glucuronic acid, the method comprising the steps of  
-optionally oxidating of 6-hydroxyls of a polysaccharide to carboxylic acid groups,  
15 when the substrate does not comprise uronic acid groups, or does contain oxidatable 6-hydroxyl groups.  
-amidating of glucuronic acid residues of the glucuronic acid comprising polysaccharide  
-hydrolysing the polysaccharide to fragments  
-optionally isolating oligosaccharide by chromatographic means.

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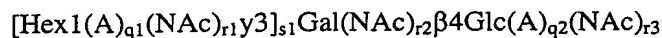
62. The method according to claim 61, wherein the amidation is performed from the polysaccharide activated by uronium type amide bond synthesis activator.

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63. The method according to claim 61, wherein the carboxylic acid is activated by methyl ester.

64. The method according to claim 61, wherein said fragments are either oligosaccharides or monosaccharides.

30 65. Helicobacter pylori binding substance



wherein q1,q2, r1, r2, r3, and s1, are each independently 0 or 1,  
35 and Hex1, and Hex2 is a hexose structures, preferably galactose (Gal) or glucose (Glc), which may be further modified by the A and/or NAC groups; y is either alpha or beta indicating the anomeric structure of the terminal monosaccharide residue with the provisions that at least r2 is 1 or q2 is 1 and

- that A indicates a glucuronamide when at least q1 or q2 is 1  
or when s1 is 0, then  
q2 is 1 and r2 is 0  
or q2 and r2 and r3 are 1  
5 or q2 and r2 are 1, r3 is 0 and A indicates a glucuronamide;  
or when s is 1 then when r2 is 1 then at least q1 is 1 or q2 is 1  
with the provision that the molecule does not comprise two non-derivatized  $\beta$ -linked  
glucuronic acid units.
- 10 66. A method of screening *Helicobacter pylori* binding substance analogs  
comprising  
  
-docking by molecular modeling a carbohydrate binding molecule of *Helicobacter pylori* *in silico*  
15 -designing binding active analogues by allowing determination of binding interactions and  
positions for possible additional binding interactions  
- determining *Helicobacter pylori* binding or inhibiting substances from the modified  
carbohydrate binding molecules
- 20 67. The method according to claim 67, wherein said carbohydrate binding molecule  
of *Helicobacter pylori* is a *Helicobacter pylori* binding oligosaccharide sequence  
according to claim 1 or 2.